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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,542	10/27/2005	Claudia Bagutti	FM-06-US	4726

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,542	BAGUTTI ET AL.	
	Examiner	**Art Unit**	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 16 September 2008.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 and 6-38 is/are pending in the application.

4a) Of the above claim(s) 10,11,14-30 and 34-38 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4,6-9,12,13 and 31-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 8/25/08.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Applicant cancels claim 5.

Accordingly, group I, claims 1-4, 6-9, 12-13, 31-33, teneurin-1 protein, are examined in the instant application.

The embodiment of claims 1-4, 6-9, 12-13, 31-33, as drawn to teneurin-2, teneurin-3 and teneurin-4 are withdrawn from consideration as being drawn to non-elected invention. Claims 10-11, 14-30, 36-38 are withdrawn from consideration as being drawn to non-elected invention.

Withdrawn Rejection

The following rejection has been withdrawn in view of the amendment: 1) Objection and 2) 112, second paragraph.

Information Disclosure Statement

The references of the Information Disclosure Statement of 08/25/08 have been considered, and a signed PTO-1449 is enclosed herewith.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-4, 6-9, 12-13, 31-33 remain rejected under 35 U.S.C. 112, first paragraph, for lack of enablement of **a method for detecting teneurin-1 signaling**, for reasons already of record in paper of 04/23/08.

The response asserts as follows:

The specification extensively details experiments evidencing that teneurin, once cleaved, is able to effectuate cellular signaling events via its cytoplasmic domain. For instance, Example 1 of the Specification demonstrates that teneurin-2 cytoplasmic domain localizes to the nucleus and co-localizes with PML, which protein is involved in a number of functions associated with transcriptional control. Example 2 of the Specification also shows that teneurin-2 is in fact biologically active and is involved in regulating Zic transcriptional activity. This example extensively details how Zic activity was significantly decreased following the expression of teneurin-2 in transfected cells, suggesting an inhibitory effect of teneurin-2 on the transcriptional activity of Zic. In addition, the immunoprecipitation experiments of Example 3 of the specification demonstrate that ponsin binds to and co-localizes together with cytoplasmic domain of teneurin-I into the nucleus. Further, teneurin is not simply active only in its uncleared state. Through microarray analysis, Example 7 shows that there are a plethora of genes whose expression products are affected either by the presence or absence of the cytoplasmic domain of teneurin. Moreover, the role that these aforementioned genes (e.g., genes listed in Tables 1 and 2) are known to have in the regulation of cell growth, differentiation, and apoptosis, overlaps with the already well-accepted functions of such proteins as PML and ponsin.

The Inventors further demonstrated in Example 4 of the Specification that the morphology of the cells expressing the contructs including the cytoplasmic domains are very

different from the ones without the cytoplasmic domain, implying an interaction of teneurin-2 cytoplasmic domain with cytoskeletal components. Similarly, Example 5 shows that clones expressing the longer form of the extracellular domain (TEY) shows a different morphology (flatter morphology) and grow in epithelial cell-like patches compared to the cells expressing the shorter teneurin extracellular domain (TE), suggesting an increase in cell-cell adhesion.

Thus, viewing the examples together, the Specification provides compelling evidence that the cleaved product of teneurin contains transcriptional activity or acts as transcriptional modulator and is translocalized into the nucleus, which undoubtedly affects signal transduction downstream.

The response has been considered but is not found to be persuasive for the following reasons:

The specification, however, does not have any data or objective evidence that a signal pathway is induced upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei. Example 3 only shows that transfected cytoplasmic domain of teneurin-1, Teneurin-1b (amino acids 156-300), binds to and translocates together with ponsin into the nucleus (p.32). Further, Examples 1-2, 4, 5, and 7 involve teneurin-2 and **not teneurin-1.** Although both of said teneurins belong to the same family of type II transmembrane proteins (the instant specification, p.1), however, the function of teneurin-1 cannot be predicted to be the same as that of teneurin-2.

One cannot predict that a signal pathway, or a signal pathway involved in cell adhesion, cytoskeleton assembly or transcription is induced upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei, because binding to ponsin

and translocation of the cytoplasmic domain of teneurin-1 and ponsin to the nucleus alone is not sufficient to indicate induction of a signal pathway, which involves a cascade of events from downstream proteins. One cannot predict which cascade of proteins, or whether there exist cascade of proteins that are modulated upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei, resulting for example in changes in cell adhesion, cytoskeleton assembly or transcription.

Further, although teneurin-1 and teneurin-2 belong to the same family of type II transmembrane proteins, however, one cannot extrapolate the function of teneurin-2 to that of teneurin-1. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. However, this is not the case for the claimed invention as no function has been elucidated for the claimed teneurin-1, and there is no indication that all members of the type II transmembrane proteins have the same function. There is no indication that teneurin-1 and teneurin-2 binds to the same target protein, which protein is transported to the nucleus and responsible for inducing a specific signal pathway. Nunes et al, 2005 (Exp. Cell Res, 305: 122-132, IDS of 08/25/08, p. 131, first column, second paragraph), teach that **teneurin-2 does not bind to the target ponsin**, which is bound by teneurin-1 cytoplasmic domain and translocated into the nucleus with teneurin-1 cytoplasmic domain. Further, relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even

opposite, biological activities. For example, Tischer et a1. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial' cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occuning PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-/ family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- beta family members BMP-2 and TGF-beta 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et a1., 1993, Bone, 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Moreover, even if teneurin-1 had the same function as teneurin-2, one cannot predict **which target** in the cell nucleus binds to teneurin-2 to produce a signaling pathway, and **which signaling pathway** is produced by the complex of teneurin-2 and its target in the cell nucleus. In Example 2, it is not clear which target protein is bound teneurin-2 cytoplasmic domain to produce reduction in the level of ApoE-luciferase reporter construct. Similarly, in Example 7, it

is not clear which target protein it bound to teneurin-2 cytoplasmic domain to induce up- or down-regulation of genes recited in Tables 1-2. Moreover, although some of the genes recited in Tables 1-2 are known to play a role in regulation of cell growth, differentiation, apoptosis, neuronal differentiation, synapse formation and function, or redox status of the cells, it is not clear which signaling pathways are induced, such that one can detect such signaling pathway, to practice the claimed method.

Concerning the unpredictability of the **in vivo existence** of such complex of cytoplasmic domain of teneurin-1 and its target protein, which is translocated into the nucleus, such as its presence in **neurons** or in **tumor** cells, the response asserts as follows:

The Examiner's conclusion that the cleavage of teneurin would not predictably be present in normal neuron or tumor cells is on the basis that mouse Ten-m protein splice variants may exist that do not allow for the cleavage of their extracellular domain of teneurin. It is evident that the Examiner has provided adequate support that such variants may exist. However, the Examiner then fails to provide a rationale for why these splice variants would be the only variants of the protein present within the cell. Further, the Examiner does not provide support as to whether such variants would even be predominant in total number in the context of normal neuronal or tumor cells. The Examiner merely concludes that since these variants exist, the predictive force of the invention is then rendered null. However, the Examiner cites no prior art reference or provides any reasonable basis to support the conclusion that the well-established manner of cleaving teneurin-1 would be conserved in some species but not others. As well, it is unclear why the intracellular cytoplasmic region of teneurin, in all normal neuronal or tumor

cells, would unable to be cleaved in light of the possibility that there may be teneurin-I variants in mice that resist cleavage of their extracellular domain.

The response has been considered but is not found to be persuasive for the following reasons:

The specification does not have any data or objective evidence that the complex of the cytoplasmic domain of teneurin-1 and its target protein, including ponsin, is found in the nucleus of the particular neurons or tumor cells. It is noted that the cytoplasmic domain of teneurin-1 for use in the examples is obtained from an **in vitro artificial condition**, and that not any cytoplasmic domain of teneurin-1 binds to and is translocated into the nucleus with ponsin. For example, the entire cytoplasmic domain of teneurin-1 cannot be used in transfection experiment for detecting interaction with ponsin, due to its self-activation (the instant specification, Example 3 on pages 31-32). Whether such particular fragment of cytoplasmic domain of teneurin-1 (amino acids 156-300) together with ponsin exists in the nucleus of neuron or tumor cells is unpredictable, because not any particular fragment of a protein exists in a particular cell in vivo. Moreover, to produce the full length cytoplasmic domain, the transmembrane protein presumably has to be cleaved first from the extracytosolic segment, which cleavage is a prerequisite for the second cleavage **within** the plane of **the membrane** to liberate the transmembrane domain from the cytosolic fragments, that enter the nucleus (the instant specification, p.2, last paragraph, bridging p.3). Whether there exists in the particular neurons or tumor cells the specific proteases and processing for producing the cytoplasmic domain of teneurin-1 is unpredictable. As shown in Nunes et al, 2005, supra, transfection of full length teneurin-1 shows the presence of intracellular domain of teneurin-1 in chicken embryo fibroblast

(figure 6, item under FLten-1 with arrow, and detected by anti-N on page 131), but said domain is absent in transfected COS-7 cells (figure 1 B, item under FL and anti-N, on page 124).

2. Claims 1-4, 6-9, 12-13, 31-33 are also rejected under 112, first paragraph, for lack of enablement of a complex of the cytoplasmic domain of teneurin-1 or **of a genus of cleaved teneurin product and a genus of cellular targets, or PML, and a method for detecting teneurin-1 signaling using said complex**, for reasons already of record in paper of 04/23/08**.**

The response asserts as follows:

Ponsin is not the only protein with which teneurin may form a complex. Rather the cleaved cytoplasmic N-terminal portion of teneurin may actually join with the protein MBD-1 and subsequently transiocate to the nucleus. S.M. Nunes et al. (2005) Exp. Cell Res. 305 122-132, 131. Moreover, the fact that some experimentation may need to take place to further determine other cellular targets of teneurin-1 does not a priori make that experimentation undue. In re Angstadto 190 U.S.P.Q. 214 (C.C.P.A. 1986).

Furthermore, even though one skilled in the art may not necessarily be apprised of the specific signaling pathways that are eventually effected by teneurin-1 signaling via the cleaved cytoplasmic domain of teneurin-1, such experimentation to elucidate these pathways is not necessarily given that claims are directed to a method to detect teneurin signaling (i.e., an assay) and significant guidance and exemplification has been given as to how to practice the methods of the invention. Even though the Examiner stated that one skilled in the art would need undue experimentation to practice the claimed invention, it is unclear why one skilled in the art is required to predict a signal pathway or identify which specific signal pathway is induced by

binding of the cytoplasmic domain of teneurin to ponsin in order to practice the claimed invention.

The response has been considered but is not found to be persuasive for the following reasons:

Ponsin and MBD-1 are not representative of the claimed genus of the target proteins.

One cannot predict, other than ponsin, and MBD-1, which other target proteins, or whether there exist other target proteins, including those in the nucleus, would complex with the N-terminal, cytoplasmic domain of teneurin-1, as claimed in claims 1-4, 6-9, 12-13, 31-32, because not any protein is complexed with a certain specific domain of a protein. Further, one cannot predict which proteins would complex with any fragment of teneurin-1, as claimed in claim 31, because not any fragment of a protein would bind to another protein. In addition, one cannot predict that PML would bind to teneurin-1, as claimed in claim 33, because not any protein is complexed with a certain specific protein.

Further, one cannot predict that a signal pathway is induced upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin or MBD-1 and their translocation into the nuclei, because binding to ponsin or MBD-1 and their translocation into the nucleus alone is not sufficient to indicate induction of a signal pathway, which involves a cascade of events from downstream proteins. One cannot predict which cascade of proteins, or whether there exist cascade of proteins that are modulated upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin or MBD-1 and their translocation into the nuclei, resulting for example in changes in cell adhesion, cytoskeleton assembly or transcription.

Moreover, the claimed method is for detecting a teneurin-1 signaling, however, without knowing which signaling pathway to detect, or whether there exists a signaling pathway induced by the complex of the cytoplasmic domain of teneurin-1 and its target protein, one would not know how to perform the claimed method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Minet et al, 1999, J Cell Science, 112: 2019-2032, for reasons already of record in paper of 04/23/08.

The response asserts that amendment of the claim to "intracellular target" would obviate the rejection. The response asserts that the teneurin-1 fragment taught by Minet et al is actually extracellular.

Minet et al teach that a soluble fragment of teneurin-1 containing the YD repeat, YD4-26, when expressed in cells, binds to heparin sulfate, as found in cell extracts (abstract, p.2024, second column, last two paragraphs).

The complex containing heparin sulfate is clearly intracellular, i.e., not outside of the cells, because it is from cell extracts. All the limitation is met.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
January 22, 2009

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643